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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,127	10/30/2001	Rekha G. Panchal	P03357US2	1718

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,127	PANCHAL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10-30-01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office action is in response to the communication filed 7-6-04.

2. Claims 1-27, 32-39 are pending in the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. In the instant case, if Applicants intend to claim priority under 35 USC 120 to Application 09/229,212 now US Patent No. 6,309,830 B1, the first line of the specification should be amended to reflect reference to this application.

Response to Arguments and Amendments

Withdrawn Rejections

5. Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

6. Claims 32-39 stand rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the same reasons of record set forth in the Office actions mailed 11-21-03 and 3-10-04.

7. Claims 8-13 and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed invention *in vitro*, does not reasonably provide enablement for practicing the full scope of the claimed invention *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the same reasons set forth in the rejection of claims 32 and 37 under 35 USC 112, 1st paragraph in the Office Action mailed 11-21-03, and the rejection of claims 13 and 32-37 under 35 USC 112, 1st paragraph 3-10-04.

Applicant's arguments filed 7-6-04 have been fully considered but they are not persuasive. Applicants argue that the instant invention is fully enabled and requires no undue experimentation to make and/or use the invention over the broad scope claimed. The claims are drawn to methods of restoring translation to any nucleotide sequence (including a nonsense mutation), or introducing a site specific mutation to any translated protein, in vitro or in vivo, or correcting any genetic defect or defects in any animal comprising introducing a nucleic acid sequence encoding a synthetic suppressor tRNA oligonucleotide derived from a human tRNA

structural gene sequence comprising a modified anticodon sequence (from the original sequence) and which anticodon will pair with a nonsense mutation or any codon different than the anticodon originally contained within the human tRNA structural gene sequence.

Applicants assert that vectors are generally available to one of ordinary skill in the art, and are useful to deliver a gene to a particular tissue, and furthermore the instant specification extensively identifies several examples of such delivery vehicles and their efficacy (esp. at pp. 16-25). Contrary to Applicants' assertions, the general teachings in the art of the availability of molecular biology products, including recombinant expression vectors, do not enable the instantly claimed invention. The adequate delivery to desired target cells in vivo, and the subsequent adequate expression of recombinant constructs such as recombinant human tRNA structural genes, are highly unpredictable and results obtained in vitro cannot be extrapolated to situations in vivo. Modes of delivery to appropriate target cells, proper formulations require undue experimentation beyond that taught in the art, and beyond that taught in the instant disclosure. The instant specification teaches a laundry list of vectors known in the art, as well as various well-known characteristics of these vectors. Such a recitation of viral, retroviral and other recombinant vectors, however, does not enable the successful delivery and functional expression of the claimed tRNA molecules in any cell in vivo, and further whereby treatment effects are provided for any genetic defect in an organism.

Applicants argue that the Examiner's assertions of target cellular toxicity in an animal is an assumption based on overly simplistic and basic theories of protein synthesis and the genetic code. Contrary to Applicants' assertions, the previously cited reference of Atkinson et al (Nucleic Acids Res. 22(8): 13-27-1334, at p. 1332) teach that the effectiveness of suppressors

differ both with respect to which codons are being read and on the contexts in which termination signals lie. And, although the identity of the particular suppressor tRNA largely determines which amino acid is inserted, it remains uncertain what happens if products other than the wild type gene product is generated. The claims read broadly on introducing any site-specific mutation into any translated protein, as well as correcting any genetic defect in an organism comprising administration of the array of tRNA constructs claimed. The specification teaches the construction of recombinant human Arg opal suppressor tRNA, its use in restoring mutated GFP function in XP12ROSV cells in vitro, and the restoration of XPAC (altered Arg 207) in DNA repair deficient, irradiated XP fibroblast cells in vitro. These in vitro examples of restoring gene function in GFP and XPAC are not representative or correlative of the ability to restore translation to any nucleotide sequence, or to site specifically mutate any protein, or to treat any genetic disease in any organism. The context of the target codon regions of the GFP and XPAC target molecules are not representative or correlative of the contexts of the array of target genes claimed (e.g. any nucleotide sequence encoding any protein to be site specifically mutated, translated or corrected in the event of any genetic defect - in vitro or in vivo). The influence of the context of the target codon region is widely known to have an influence on the ability of a tRNA to insert the desired amino acid (see Atkinson as cited above; see also Beir et al, § Codon Context Effects: "'It was found that changes at each position completely abolished or greatly reduce ... suppression by tRNA..., indicating that this tRNA species needs a very specific codon context for its suppressor activity." Beir also teaches that this context can involve more complex signals like stem-loop or pseudoknot structures for proper tRNA function. *Id.*) Therefore, the Examiner's assessment of unpredictability for the broad scope claimed, regarding both the

unpredictability to insert a desired amino acid in vivo, and the unpredictable effect of tRNA overexpression on a target cell in vivo, is neither simplistic nor misplaced.

In addition to the uncertainty of target cell delivery and appropriate expression in vivo, the ability to produce high copies of recombinant tRNA suppressor molecules varies, depending upon vector choice, and must be determined empirically for a particular suppressor molecule and corresponding vector (e.g. see Capone et al, EMBO J., 4(1): 2130221, at p. 220, second to last paragraph in discussion: "It is likely that our inability to obtain such a virus stock is due more to the presence of opal suppressor tRNA gene as part of a high copy replicative recombinant vector, resulting in deleterious levels of suppressor activities."

Applicants also assert that tRNAs do not mediate protein termination, but rather that translation termination involves an interaction between elongation factors, ribosomal RNA loops and the structure of the mRNA being translated. The role of tRNAs in translation is not being asserted here, and, according to Applicants' representative's own statements (p. 13-14 of remarks filed 7-6-04), these factors all contribute to the variability of the tRNA suppressor activity: "The precise molecular mechanism explaining the influence of downstream nucleotides and secondary structures on stop codon readthrough involves tRNA selection through stabilization of the tRNA-mRNA interaction by stacking effects, interaction between the stop codon and the rRNA, and interaction between the stop codon and the polypeptide chain release factor." The examples provided of the correction of two target nucleotides using a single tRNA suppressor in cells in vitro does not enable the broad scope claimed, especially considering the complexity of this suppression process.

Applicants also argue that efficiency of suppression correlates with levels of suppressor tRNA achieved in a particular target cell or target tissue, and therefore that low levels of expression of suppressor tRNAs will lead to low levels of suppression and protein readthrough and will not affect the function of normal proteins. The ability to control the level of expression of a recombinant molecule in a target cell in vitro or in vivo has not been demonstrated in the instant disclosure, however, and further whereby a high level of expression is avoided, yet a low level of expression provides for treatment effects. Applicants argue that low level expression of various enzymes (such as factor IX or adenosine deaminase) provides for treatment effects, and a correlation is made with these examples and the non-enzymatic protein, globin. The required amount of enzyme potentially obtained with the tRNA suppressor therapeutic approach, to provide a target cell with the necessary corrected polynucleotide for providing treatment is not necessarily representative of the ability to provide a required amount of non-enzymatic protein using this therapeutic approach. Furthermore, factor IX is involved in a cascade process, and is even less comparable, if at all, to what is required in a different biological context, such as instantly claimed. The toxic effects, or treatment effects provided for targeting a particular codon using a particular tRNA cannot be generalized and requires undue experimentation beyond that taught in the instant disclosure.

New Rejections

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7, 12-21, 23, 22 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "[A]n oligonucleotide sequence..," the actual patentable subject matter in this case is unclear, since one can not separate an oligonucleotide from it's nucleotide sequence. Therefore, it is unclear if Applicants were intending to claim merely the sequence of the oligonucleotide, or an oligonucleotide comprising the recited sequence. Additionally, claim 1, line 9, recites the phrase "said oligonucleotide," this phrase is vague and indefinite since it is unclear if the instant claim is drawn to an oligonucleotide sequence or an oligonucleotide having a sequence.

Claims 2-6, and 21 recite the phrase "The oligonucleotide of claim 1," this phrase is vague and indefinite since claim 1 is directed to an "oligonucleotide sequence," and not specifically to an oligonucleotide.

Claims 7 and 12 recite "SEQ ID NOS: 1-10 and their complements." The metes and bounds of the term "complements," as recited in the instant claims is vague and indefinite since it is unclear if applicants intended for this term to encompass complements of any particular length or any particular percent complementarity.

Claim 13 and 27 recite the "sequence of claim 1," this phrase is vague and indefinite since it is unclear which "sequence" Applicants are referring to, the "oligonucleotide sequence," the "human tRNA structural gene sequence," or the "sequence encoding an anticodon region."

Claims 14-20 recite phrase "the nucleotide sequence of claim 1," this phrase is vague and indefinite since it is unclear which "sequence" Applicants are referring to, the "oligonucleotide sequence," the "human tRNA structural gene sequence," or the "sequence encoding an anticodon region."

Claims 22 and 27 recite a method of introducing a site specific mutation to a translated protein by introducing a synthetic suppressor tRNA encoded into a cell. It is unclear how a tRNA molecule can site specifically modify a translated protein. Replacing "translated protein" with -nucleotide sequence encoding a protein- would potentially be remedial.

In claim 27, line 3, "said cell" unclear since neither claim 27 nor claim 1, from which it depends, recite cell. Replacing "said" with -a-would be remedial.

Claims 38-39 recite "a suppressor tRNA sequence" according to claim 1, there is lack of antecedent basis for this limitation in claim 1.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6, 8-11, 13-25, 27, 32-35, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

The instant claims are drawn to any human tRNA structural gene sequences, including all polymorphic and allelic variants of said gene sequences. Although there are multiple known human tRNA structural genes in the art, Applicants were not in possession of the full scope of human tRNA structural genes encompasses by the instant claims. At the time of filing, one of skill in the art would have been able to predict the structures of the full scope of compounds encompassed by the claimed genus of compounds that include all allelic and polymorphic variants of human tRNA structural genes. The basis of the instant invention requires the prior knowledge of the structure of a mutant tRNA gene that is associated with the pathogenesis of a certain disease, wherein said mutant tRNA does not provide the correct protein during translation. Without prior knowledge of the mutant tRNA the skilled artisan would not be able to practice the claimed invention.

Moreover, if the scope of the human tRNA structural genes recited in the instant claims are not limited to those genes that were previously known in the art as of the filing date of the instant application, further experimentation would be required to fully envision the full scope of the claimed invention.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed

invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Additionally, see MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Therefore, since further experimentation would be required to characterize the nucleotide sequence of the full scope of the human tRNA structural genes encompassed by the instant claims, Applicants were not in possession of the full scope of the claimed invention at the time of filing of the instant application.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3, 5, 8-10, 13-16, 20-24, 27 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Capone et al.

14. Since claim 1 and those claims dependent thereon are drawn to an oligonucleotide sequence, and not specifically to an isolated oligonucleotide of a total length of less than 150 nucleotides, the following prior art is applied to the extent that the instant claims are directed merely to a sequence that is disclosed in the prior art.

Capone et al (EMBO J. 4(1): 213-221, 1985) teach compositions and methods of introducing a site specific mutation into a polynucleotide encoding a protein, and methods of restoring translation to a nucleotide sequence which includes a nonsense mutation in a cell in vitro comprising introducing to said cell an adeno viral vector encoding a nucleic acid sequence encoding a synthetic suppressor tRNA oligonucleotide comprising a recombinant human tRNA structural gene sequence comprising no more than twenty 3'flanking residues and no 5' flanking residues, encoding an anticodon region for pairing with mRNA, wherein the anticodon sequence has been modified to recognize a codon different than the originally recognized one, which original anticodon region encoded an amber or ochre nonsense mutation, and which was changed to encode a serine tRNA (see abstract, figure 1 on p. 214, text on p. 216-219).

Claim Objections

15. Claims 3, 4 and 23 are objected to for the following reasons:

In claim 3, line 1, "an" following "encodes" should be replaced with -a--.

In claim 4, line 2, "said" should be replaced -the--.

In claim 23, line 2, "an" should be replaced with -a--.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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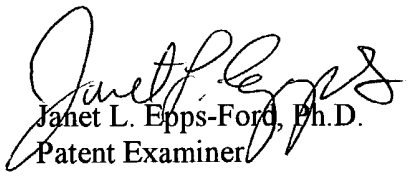

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